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Green Synthesis Approaches In Metal Nanoparticulat -es Preparation Drug Delivery

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ABSTRACT:

"Green synthesis approaches have drawn a lot of attention in the preparation of metal nanoparticles because they may reduce the environmental impact of nanoparticle synthesis." These methods reduce the need for hazardous chemicals and energy-intensive processes by utilizing natural sources such as microbes, plant extracts, and eco-friendly materials. Utilizing green synthesis techniques to generate metal nanoparticles has been shown to be a biocompatible and ecologically sustainable strategy with substantial potential in therapeutics and medication delivery. With a focus on how they might improve targeted drug delivery to specific regions of action, reduce systemic toxicity, and increase therapeutic efficacy, this work focuses on the environmentally friendly production of metal nanoparticles and their use in sophisticated drug delivery systems. Metal nanoparticles are commonly prepared using green synthesis techniques such as plant-mediated synthesis, microorganism-based synthesis, and bio-inspired synthesis. Numerous benefits come with these methods, such as decreased toxicity, less waste being produced, and the possibility of cheaper, large-scale production. They also have potential uses in several other areas, including environmental remediation, drug delivery, sensing, and catalysis. The goal of this review is to provide an overview of the current state of green synthesis approaches utilized in the preparation process for metal nanoparticles, emphasizing their benefits, drawbacks, features, and preparation process for these particles, their description, their type, the factors that influence them, their applications, their toxicity, and the difficulties they present.

KEYWORDS: Green synthesis, Metal nanoparticles, Biomedical applications, Bioactive compounds, Drug delivery systems.

INTRODUCTION:

"The use of science to manipulate matter at the molecular level is known as nanotechnology." Among other fundamental and applied frontiers, surface-enhanced Raman scattering (SERS), nanobiotechnology, bionanotechnology, quantum dots, and applied microbiology have all seen great progress in the realm of materials science and engineering.[1] With the ongoing efforts and outstanding results in alternative nano-based medicines, nanotechnology and nanoscience are significant disciplines for the advancement of contemporary society.[2] Nanotechnology is becoming more and more important in fields including catalysis, optoelectronic devices, photoelectrochemical applications, nonlinear optical devices, drug-gene delivery, chemical industry, electronics, and space sectors.[1]

Nanoparticles are colloidal structures formed by synthetic or semi-synthetic polymers. A nanoparticle matrix is used to disperse, entrap, encapsulate, or bind the drug. The primary goals of manufacturing nanoparticles as a delivery method are to control particle size, surface characteristics, and the release of medicinal chemicals. This allows the medicine to act on specific sites at the therapeutically ideal rate and dosage schedule. Nanoparticles are of tremendous interest because they differ chemically and physically from bulk materials with the same chemical composition in terms of optical absorption, mechanical, biological, and sterical characteristics, catalytic activity, thermal and electrical conductivity, and melting temperature. This is due to their extremely tiny size and high surface-to-volume ratio.

The development of sustainable technology for the environment, humanity, and the future depends heavily on nanoparticles. Plant-based nanoparticle synthesis is a method of green chemistry that combines nanotechnology with plant biotechnology methods. Plant extracts are used in the bioreduction process to produce nanoparticles from metal ions. Sugars, terpenoids, polyphenols, alkaloids, phenolic acids, and proteins are examples of plant metabolites that are required for both metal ion reduction and subsequent nanoparticle stability. Numerous revolutionary potentials in the battle against neurological diseases, cancers of all kinds, and other illnesses are presented by nanomedicine. With fewer negative effects, the diverse endemic diseases have been efficiently controlled by biosynthesized nanomaterials. Utilizing natural products has become more common, and active plant extracts are commonly available. Natural products are becoming more and more popular, and researchers are always testing active plant extracts in the hopes of finding new medications. Consequently, biological components obtained from plant sources as extracts are used in green synthesis. demonstrating an advantage over chemical processes.[3] Metal nanoparticles possess a broad variety of significant applications in pharmacy and medicine. The most often employed nanoparticles in the developing multidisciplinary field of nanobiotechnology and biomedical applications are those made of gold and silver.[1]

History:

The diachronic glass Cup of Lycurgus was created in Rome during the 4th century, marking the first application of nanoparticles. It was employed to give vessels a shiny appearance in Mesopotamia (Iraq) in the ninth century. The distinctive metallic luster of gold or copper is still present in most pieces of medieval and Renaissance ceramics today. In ceramics, nanoparticles are created by combining copper and silver salts and oxidizing them with vinegar.[4, 5] The first evidence of metallic nanoparticles dates back to the 14th and 13th centuries BC, when glassmaking with metals was first practiced by the Egyptians and Mesopotamians. This initiates the process of creating metallic NPs by chemical means.[6] The 1857 Relationship experiment between gold and other metals with light and Faraday's seminal work both define the characteristics of nanoparticles.[7, 8]

MERITS OF METAL NANOPARTICLES:

1. Surface increased Raman scattering.
2. Rayleigh scattering enhancement.
3. Powerful absorption of plasma.
4. Imaging of biological systems.
5. Determining the chemical composition of a metallic nanoscale substrate.[9]

DEMERITS OF METAL NANOPARTICLES:

1. Particle instability:

Because nanomaterials are located in areas of high energy local minima and are thermodynamically unstable, they are susceptible to transformation. This results in poor corrosion resistance, quality degradation, and the primary concern—that is, it becomes harder to maintain the structure.

2. Impurity:

The development of nitrides and oxides during the synthesis of nanoparticles might be exacerbated by an impure environment. Because of their extreme reactivity, nanoparticles can also have a high chance of impurities. It is best to create nanoparticles by encapsulating them in a solution. As a result, eliminating contaminants from nanoparticles becomes challenging.

3. Hazardous to biological systems:

It has been documented that nanoparticles are toxic, carcinogenic, and irritate skin since they show through the cell dermis.

4. Explosion:

Exothermic combustion can result because fine metal particles have an explosive potential.

5. Synthesis difficulty:

Nanoparticles should be encapsulated during synthesis because it is very difficult to maintain the nanoparticle's size in solution form.[10]

METALLIC NANOPARTICLES' CHARACTERS:

1. Higher energy at the surface.
2. They have a large surface area-to-volume ratio in comparison to bulk materials.
3. The concept of quantum confinement.
4. Excitation via Plasmon.
5. A higher quantity of kinks.[11]

PREPARATION METHODS FOR METAL NANOPARTICLES:

a) When producing metallic nanoparticles, consider the following:

The following suitable methods should ideally be used to create metallic nanoparticles:

1. Simple to duplicate.
2. Affordable and easily accessible.
3. Employ the fewest possible reagents.
4. Could influence the particle's form.
5. Make use of a reaction temperature that is almost ambient.
6. Reducing the amount of waste and byproducts produced. [9]

b) The various synthesis methods that can be used to create metal nanoparticles include:

• Using a bottom-up strategy:

The bottom-up approach uses small building blocks, such as molecules and atoms, to make nanoparticles. Alternatively, atoms can self-assemble to form new nuclei, which can subsequently expand through a variety of chemical and biological processes into particles with nanoscopic dimensions.

• Using a top-down strategy:

This process creates nanoparticles by using appropriate lithographic processes, such as crushing, spitting, and milling, on suitable bulk material that has been minimizes to small entity. Nanoparticles can be manufactured with exact control over pH level, temperature, plant extract concentration, metal salt solution, and incubation period. Siddiqi and colleagues (Siddiqi and Husen 2016) [12] conducted a review on the creation of palladium and platinum nanoparticles. They also outlined the entire process of creating nanoparticles and discussed their possible uses in biosensors, medicine, diagnostics, catalysts, and pharmaceuticals (Fig. 1). [13]

1. Synthesis of nanoparticles by physical method:

This covers nonochemistry, laser ablation, radiolysis, UV irradiation, and other methods. During the physical synthesis process, it is found that once metal atoms evaporate, they gather as tiny clusters of metallic nanoparticles through reorganization and condensation on various supports.[14] Physical methods enable us to generate highly pure and well-defined nanoparticles. However, these procedures typically require highly advanced equipment, chemicals, radiative heating, and a high power requirement—all of which raise the cost of operation.

2. Synthesis of nanoparticles by chemical method:

Reducing metal ions in solution with chemicals is another way to create nanoparticles. According to the chemical reaction mixture, metallic ions may promote the nucleation or aggregation process to produce tiny clusters of metals. As reducing agents, common materials include hydrogen, sodium borohydride, and hydrazine additionally.[15] certain stabilizing agents are also utilized, including co-polymer micelles, cellulose, natural rubber, and synthetic or natural polymers like chitosan. Due to the hydrophobic nature of these substances, organic solvents have to be employed. The production size of these chemicals is restricted due to their non-biodegradable nature and toxicity. Furthermore, some of the hazardous substances may contaminate the nanoparticles' surface, rendering them inappropriate for use in specific biomedical applications.[16] Researchers and scientists are concentrating on alternate processes for the production of metal nanoparticles to overcome all of the shortcomings of physical and chemical approaches.

3. Synthesis of nanoparticles by biological method:

The process of creating metallic nanoparticles by biogenic synthesis has garnered a lot of interest lately. Plants and microorganisms are applied in the biogenic synthesis process to create nanoparticles.[17] Comparing the biosynthetic process to certain other physicochemical techniques of manufacturing, it is possible that the latter yields nanoparticles with a more precisely defined size and shape. [18] The cost of manufacturing material based on microorganisms is sometimes higher than that of producing material based on plants, even though a microbial-based synthesizing procedure is simple to scale up, ecologically conscious, and in accordance with the usage of products for medicinal purposes. Plant-based processes for synthesis have several advantages over conventional chemical as well as physical procedures. First, they don't involve the employing of dangerous substances, extreme temperatures, or forces. Secondly, they are more inexpensive, easier to scale up, and environmentally benign.[19] Because of their reducing or antioxidant properties, which result in a proportional decrease in metal nanoparticles, bacteria, fungus, algae, and plants have been used in the biological creation of metallic nanoparticles. Additionally, it has been found that the creation of nanoparticles using microbes isn't suitable for huge-scale manufacturing due to the need for extremely aseptic conditions and specific maintenance; on the other hand, the synthesis of nanoparticles using plants is more advantageous than the synthesis of microorganisms because it is a simple process that can be scaled up easily and doesn't require additional maintenance of cell culture. [20] Utilizing plant extract instead of microbes for nanoparticle production also lessens the need for preparing culture media and isolating microorganisms, making it more feasible and cost-effective. Because plant-mediated production is a single-step procedure, research on plants is rapidly expanding, whereas microorganisms may eventually lack the ability to make nanomaterials due to variation. [21] Many synthesizing processes have been established, such as thermal decomposition in organic solutions and chemical decreases in metal ion content in aqueous solutions with or without stabilizing agents. [22]

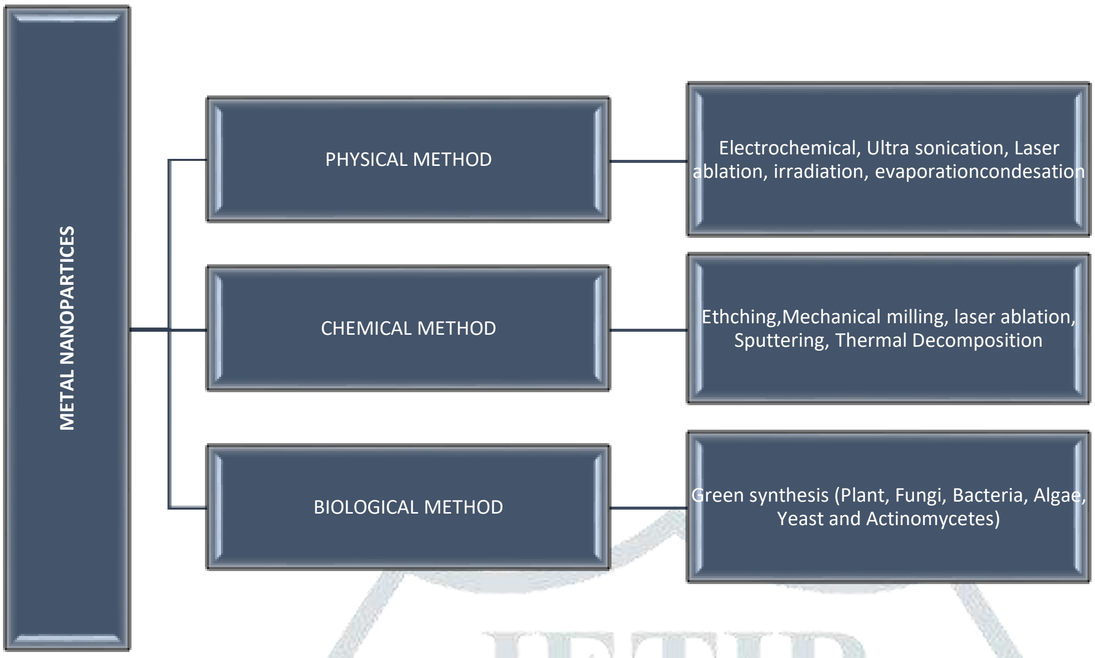

Fig. 1 Different techniques for creating nanoparticles. [22]

- **Green synthesis approach for metal nanoparticles:**

Scientists confirmed that, in contrast to previous physicochemical techniques, biologically generated nanoparticles exhibit higher levels of pharmacological activity. When various influencing factors like pH, warmth, retention duration, and blending proportion are controlled, green metallic nanoparticles produced by various plants such as leaves of neem (Azadirachta indica) are stable and easily monodispersed.[23] Using a range of medicinal plants, metallic nanoparticles were green-produced and have shown the most important therapeutic capabilities, including antibacterial, insecticidal, antioxidant, repairing wounds, anti-diabetic properties, immunomodulatory agents, liver-protective, and cancer-fighting properties. Synthetic metallic nanoparticles derived from medicinal plants are highly advantageous for the biomedical industry.[24] Methane, nitrous oxide, and carbon dioxide emissions were reduced by green nanoparticles (GNPs) derived from various plants. This is a key idea for using green nanotechnology in agriculture to lower fertilizer costs and their negative effects on the environment. Furthermore, farmers who are concerned about their health can use green nanoparticles to boost agricultural output.[25] Plants naturally contain a wide variety of phytochemical components.

These are low-cost and environmentally friendly variables. The substantial significance of environmental heavy metal detoxification is highlighted by green-manufactured nanoparticles. Given how many toxic metals in land and water, green nanosized particles can help minimize the harmful effects of metals in the surroundings.[26] Since the various plant's parts—roots, trunk, leaves, seeds, and fruit—contain a multitude of phytochemical compounds, the green production of metal nanoparticles is not only less expensive and ecologically friendlier than other biological processes, but it is also more efficient.[27] Selected plant components must be squeezed, filtered, and treated with certain salt solutions before being cleaned with tap or distilled water to synthesize green nanoparticles. The solution's altered color verifies the presence of the manufactured nanoparticles. Metal nanoparticle synthesis depends on phytochemicals such as gallic acid (GA), ellagic acid, and other phenolic acids. Phytochemical factors are agents that aid in the reduction and stabilization of metal nanoparticles that are formed. [28]

The application of a set of rules to the creation and manufacturing of diverse chemical products that reduce the usage of dangerous substances and have a negligible detrimental effect on the environment and public health is known as "green chemistry."[29] Green nano-biotechnology is the method of creating stable nanoparticles by biological means.[30] Green chemistry principles were a breakthrough when they were applied to nanotechnology since they reduced the risk factor.

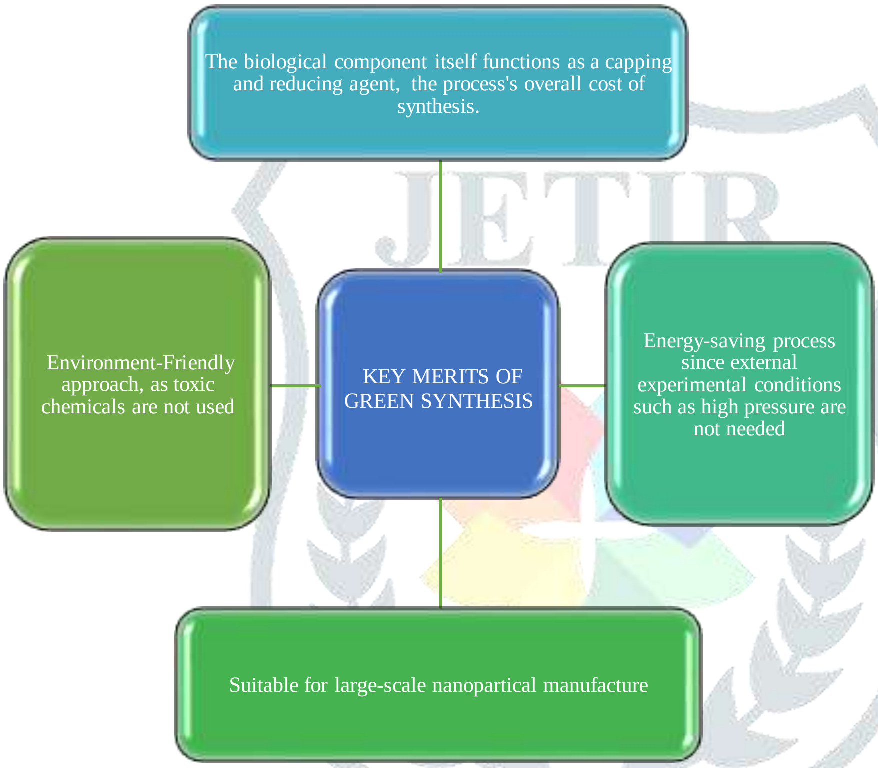

Fig. 2 The main advantages of green synthesis. [31]

- **There are primarily 12 concepts in green chemistry, which are as follows:**

1. **Prevent waste:** The main goal of green nanotechnology is to create greener nanoparticles by lowering pollution and waste creation.
2. **Production of safer chemicals and goods**: This method typically creates nanoparticles with the required characteristics and little to no toxicity.
3. **Designing a less dangerous chemical synthesis:** To produce more effective, less poisonous products.
4. **Use renewable feed stocks:** It is preferable to use environmentally safe and renewable raw materials for production as opposed to those that harm the environment.
5. **Catalyst utilization:** Products produced with the help of efficient catalysts are far greener.
6. **Reduce derivatives:** Minimize derivatives by avoiding needless derivatization.
7. **Atom economy:** Producing environmentally friendly goods should be done in a way that maximizes the share of raw materials.

8. **Pollution prevention and reduction:** Green nanotechnology uses fewer harmful chemicals, reducing the likelihood of contamination. Analytical techniques need to be enhanced to provide actual time-procedure control and supervision before the generation of hazardous chemicals. Refrain from using chemical derivatives; do not add needless blocking or protective agents to your synthesis procedure.

9. **Improving energy effectiveness:** The chemical process takes place under normal pressure as well as temperature settings using specialized production techniques.

10. **Ensure more safe reaction conditions as well as solvents:** Toxic chemicals, separation agents, and hazardous solvents are not used. Most frequently, the bottom-up strategy is thought to improve material efficiency and remove stages. The solvents of choice are methanol, acetone, ethanol, and water.

11. **Design for degradation:** Create products that will break down at the end of their useful lives because not everything can be recycled.

12. **Decrease the chance of accidents:** When choosing materials for a chemical process, care should be taken to lower the risk of chemical accidents like fires, explosions, and other catastrophes.

Physical as well as chemical methods involve the usage of hazardous substances and solvents. There is a substantial power requirement for these procedures. On the other hand, safe, non-toxic chemicals are used in the more environmentally friendly green synthesis of nanoparticles. The green chemical strategy appears to produce more stable and advantageous nanoparticles. The principal organisms used in this method are microorganisms, plants, algae, bacteria, yeast, and fungi. The green method of nanoparticle production is straightforward, inexpensive, easy to define, and has a lower failure rate. The primary benefit of green synthesis is its ability to produce nanoparticles with lower toxicity, which in turn renders them less detrimental to the environment.

A consequence of sustainable development that satisfies the demands of future generations is green synthesis. By preserving the natural balance of the ecosystem, this method minimizes the consumption of naturally occurring resources, lowers pollution, and enhances environmental quality.

- **The green synthesis technique's advantages are:**

1. Easy to use, inexpensive, and environmentally friendly since it doesn't require the use of dangerous chemicals or solvents.
2. In contrast to conventional procedures, it is free of pollution.
3. Promotes waste prevention.
4. It decreases the generation of derivatives.
5. Does not call for high pressure or temperature.
6. Prevent mishaps from occurring.
7. Utilize readily available and sustainable raw resources.
8. Successful in producing nanoparticles on a massive scale.

- **A drawback to green synthesis:**

1. The risks to human health have increased because of nanotechnology.
2. The toxicity and bioaccumulation of nanoparticles in the environment have not been extensively studied.
3. The tiny size of NPs makes it easy for them to enter the body and cause fatal diseases and breathing problems.
4. Chemically produced nanoparticles are still more widely used in industry than green synthesis. [32]

- **The basic steps in the production of green synthesis nanoparticles are as follows (Fig. 3):**

1. First phase: Obtaining the preliminary salt, an origin of metallic ions, and the chemical reaction media, either a water-based extraction of plant materials or an incubation phase for microorganisms.

2. Activation phase: Here, nucleation sites are created and metal ions are chemically reduced, allowing nanoparticles to form and grow.

3. Growth phase: Temperature, concentration, kind of substance, pH, and reaction time are some of the variables that affect the spontaneous fusion of small neighboring nanoparticles into larger particles, or aggregates.

4. Termination phase: The compounds involved in the reaction help stabilize and improve the characteristics of the nanoparticles, and their final shape is established. 33 Figure 3. Phases for the green synthesis of metal nanoparticles.[33]

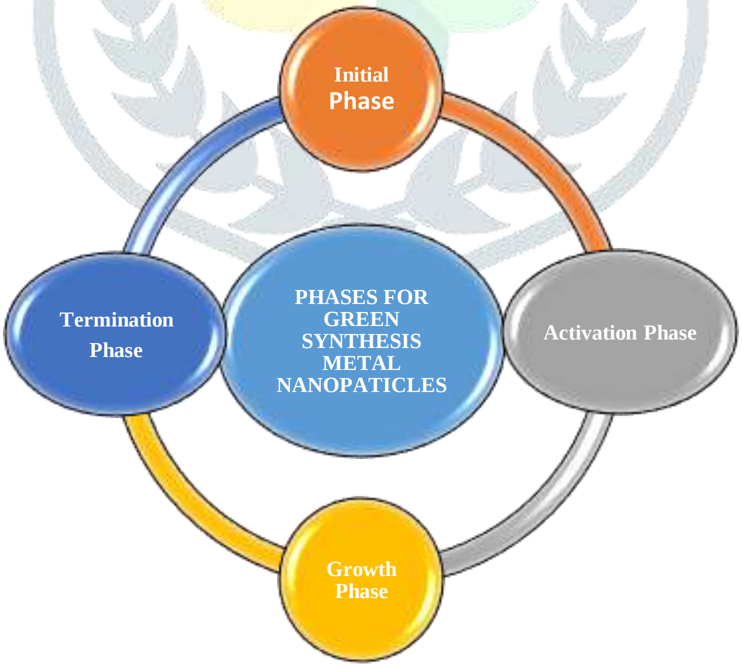

Fig. 3 Phases for green synthesis metal nanoparticles [33]

EVALUATION PARAMETERS OF METAL NANOPARTICLES:

a) Absorbance spectroscopy:

Because metal nanoparticles have bright colors that are apparent to the unaided eye, spectroscopy helps characterize them. Qualitative data regarding the nanoparticle can be acquired using this method. The measurement of absorbance is done by using Beer's law. Extinction coefficient (A) and nanoparticle concentration © can be derived based on path length.[1]

b) Infrared spectroscopy:

This technique can reveal details about the organic coatings that envelop metallic nanoparticles. It also provides important information for comprehending the metal nanoparticle surface structure.

c) The transmission electron microscopy (TEM):

In terms of understanding more about the size, shape, crystallinity, and interactions between individual particles of nanomaterials, this technique is also widely employed to characterize them. The TEM is a tool for chemical and structural characterization with great spatial resolution.

d) Scanning electron microscopy (SEM):

SEM is a strong method that can photograph a material's surface at a resolution of about 1 nm. Second-order electrons with an energy level of less than fifty eV are created. when an incident electron beam interacts with the specimen. SEM can provide details regarding the sample's nanoparticle purity.

e) AFM:

For nonconductive nanomaterials, this method works better. It’s typical lateral resolution is about 1 nm, and its vertical resolution is less than 0.1 nanometer. It offers in-depth knowledge of the atomic level, which is required to learn chemical bonding and electrical structures in molecules as well as atoms.

f) XRD:

It is a practical and popular method for figuring out crystalline materials' crystal structures. The strain and size of a nanocrystal are directly correlated with the diffraction line widths. The lack of order at long range around a large portion leads the path width to widen as the nanocrystal's size diminishes.[9]

g) FTIR:

Infrared red light is used to expose the material to infrared analysis. A fraction of the rays travel through the sample and are absorbed by it in part. The spectrum provides characteristics of the sample chemicals, such as absorbance / transmission, as a result of wavelengths. Fourier Transform Infrared Spectroscopy (FTIR) is a practical, economical, easy, and safe approach for determining the contribution of biological molecules in the reduction of nanoparticulate (from the silver nitrate to silver).

h) UV visibility spectrophotometer:

Using UV-Vis absorption spectroscopy, nanoparticles can be measured in sizes between 2 and 100 nm, with a wide range of metals having different sizes at different levels. Typically, wavelengths between 300 and 800 nm are employed to study the nanoparticles that UV-Vis absorption spectroscopy has confirmed. The point spectrum in the visible area is produced by the significant absorption of metallic nanoparticles generated under specific salt conditions. According to earlier research findings, nanoparticles with sizes between 2 and 100 nm should be classified according to their absorption of wavelengths between 200 and 800.

i)Annular dark-field imaging (HAADF):

This technique identified how nanoparticles interacted with bacteria and revealed details about the size distribution of these interactions.

k) Intracranial pressure (ICP) spectrometry: The metal concentration in both the original and deionized nanoparticle solutions was used for confirmation. Coupled emission spectroscopy (ICP-ES) and combined plasma mass spectrometry (ICP-MS) are used in experiments to measure the concentrations of metal nanoparticles. [34]

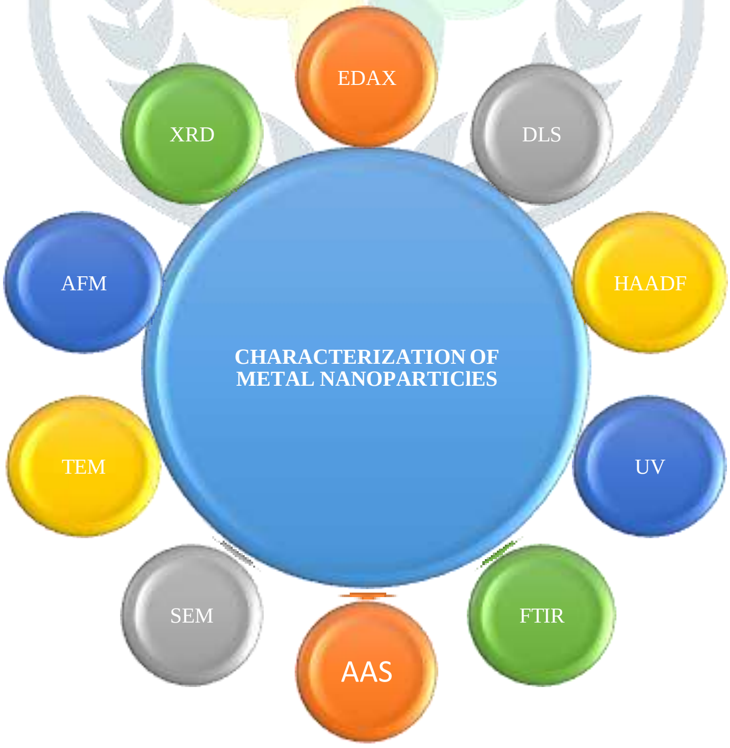

Fig. 4 Characterization of metal nanoparticles. [34]

FUNCTIONALIZATION AND STABILIZATION OF METAL NANOPARTICLES:

Typically, the high chemical activity of designed nanoparticles with a developed surface causes unwanted, powerful, and often irreversible reactions like aggregation. Aggregation reduces particle reactivity by lowering the particular area of the surface & interfacial energy that is free. Thus, it is important to enhance the stability of the developed nanoparticle throughout its entire life cycle, including storage and transportation. Almost all stabilization techniques, as noted by Stubbs and Gilman, involve dispersant molecules like polyelectrolytes or surfactants, which alter the chemistry and physics of the nanoparticle surface while also producing a significant waste stream. Therefore, in order to avoid contamination and the ensuing detrimental effects on the environment, it is imperative to search for biocompatible—that is, non-immunogenic, non-toxic, and hydrophilic stabilizing agents—as well as ecologically benign stabilization and functionalization routes.

In addition to functionalizing the nanoparticles for the intended applications, a variety of stabilizing chemicals are available to stop the particles from aggregating. Conversely, however, hazardous substances and harsh reaction conditions are typically unsuitable for biological and biochemical applications. These days, metal nanoparticles can be functionalized and stabilized using a number of "green" stabilizing chemicals that won't harm biological systems or the environment.[35]

TYPES OF METALLIC NANOPARTICLES:

1. Nanoparticles of silver:

Silver exhibits therapeutic properties for an extensive array of illnesses. Top-down and bottom-up methods make it simple to create silver nanoparticles. Two essential ingredients are needed to make Ag nanoparticles: a reducing agent and a silver metal ion solution. Proteins, amino acids, vitamins, and a variety of medicinal plants are employed to make silver nanoparticles. Changes in the solvent and capping or reducing agents can also affect the shape of the produced nanoparticles. The size of the nanoparticles was mostly regulated by the medium's pH. The therapy for cancer makes extensive use of silver nanoparticles. They work well in the medical field because they have antibacterial and antimicrobial properties. Their strong antioxidant and catalytic activities are also well known. Ag nanoparticle research benefited from the publication of several works.

A variety of microorganisms, such as Bacillus subtilus and Bacillus amylaceous, can be used to create Ag nanoparticles, which are expected to have diameters of less than 140 nm. Eucalyptus hybrida, Hibiscus rosa sinensis, Nelumbo lucifera, and other plants can be efficiently used to create Ag nanoparticles with the aid of a silver nitrate solution. It is well known that olive leaf-derived Ag nanoparticles have antibacterial qualities. With TEM and FTIR spectroscopy methods, these can be further described. Ag nanoparticles that were spherically shaped and polydisperse were found at 427 nm in wavelength.

2. Nanoparticles of gold:

These nanoparticles' special qualities include strong scattering and absorption, minimal toxicity, and compatibility. Both the bioanalytics and medical fields make extensive use of them. Au nanoparticle formation is aided by a few biomolecules found in the plant extract, such as flavonoids, phenols, and proteins. Surprisingly, Au nanoparticles were found to be spherical, icosahedral, decahedral, and triangular.

Silver and gold nanoparticles are used in light-emitting diodes. Aloe vera and geranium leaf extracts were used to create Au nanoparticles. Au nanoparticles are frequently generated using algae and bacteria. It was reported that gold nanoparticles were created using Tamarindus indica leaf, Emblica officinalis (Indian gooseberry), and fungus. They have antioxidant, antimicrobial, and anticancer properties. Additionally important to medication delivery systems, gold nanoparticles aid in the identification of protein-protein interactions.

3. Copper nanoparticles:

Toxic reducing agents and organic solvents are typically used in the physical and chemical synthesis of Cu nanoparticles. Since copper oxidizes quickly, creating stable Cu nanoparticles is a somewhat involved procedure. Their high surface area facilitates easy bacterial interaction, which gives them antibacterial qualities. Nematicidal properties are also displayed by them.

There aren't many studies available on the manufacture of Cu nanoparticles; ascorbic acid, microbes, and plant extracts are typically employed as reducing agents. Although produced Cu nanoparticles have low conductivity because of the presence of oxide layers, metallic copper typically has strong conductivity. Electronic devices make extensive use of Cu nanoparticles. By reducing copper ions, plant extracts such as those found in aloe vera can aid in the creation of Cu nanoparticles. The colloidal heat combination procedure was used to create copper oxide nanoparticles of various sizes.

4. Palladium nanoparticles:

Palladium nanoparticles are created by reducing palladium salt with a reducing agent; this is a more effective synthesis than ion exchange, thermal breakdown, chemical breakdown, etc. Pd nanoparticles can efficiently remove harmful contaminants and dyes.

5. Platinum nanoparticles:

Pd and Pt are both costly, highly dense metals. Pt nanoparticles are essential to the synthesis and administration of drugs. Since they are utilized in the development of specific chemotherapeutic medications like cisplatin and carboplatin, they are useful in the treatment of cancer. They're employed in sensors and are also employed as antibacterial agents.

6. Zinc oxide nanoparticles:

ZnO is a semi-conducting oxide of metal of the n-type with pyroelectric and piezoelectric characteristics. These qualities lead to strong catalytic activity and high semiconducting capabilities, such as wound healing. Plant extract, hydrated zinc sulfate, and oxide of zinc are usually combined to create them. A color shift in the solution indicates the production of nanoparticles. It takes a long time to produce ZnO nanoparticles from bacteria in a green manner, and reports of this synthesis from algae are few. It looked as though the ZnO nanoparticles made from fungus were spherical. Research was done on the manufacture of ZnO nanoparticles utilizing Lactobacillus plantarum, B. licheniformis, and Azadirachta indica. Zinc oxide nanoparticles are both affordable and biocompatible. These nanoparticles may therefore find application in medicine delivery and bioimaging. Lower quantities of zinc oxide nanoparticles kill human cancer cells, but higher concentrations are comparatively safe. These NPs aid in the management of diabetes and cholesterol, as well as the management of infectious infections.

7. Titanium oxide nanoparticles:

These particles are often used in food additives, coatings, cosmetics, and other industries. They have qualities that are antibacterial, antifungal, and antimicrobial. Their photocatalytic activity is good. Using Aspergillus flavus, TiO_2 nanoparticles with antibacterial properties were created. Bacillus mycoides was also used to create these nanoparticles, which are used in solar cells.

8. Lead sulfide nanoparticles:

The NS2 and NS6 bacterial strains were responsible for the extracellular production of PbS nanoparticles. These nanoparticles function well as antibacterial agents and show photocatalytic activity.

9. Nanoparticles of iron oxide:

The diameter of these particles varies from one to one hundred nanometers. Iron oxide nanoparticles come in two primary forms: magnetite and its oxidized version, maghemite. Typically, they display superparamagnetic characteristics. Brown seaweed, Carica papaya, and other ingredients were used to create magnetite (Fe_3O_4) nanoparticles. Monocotyledon and dicotyledon plants, as well as Ocimum sanctum, were used to create iron oxide nanoparticles. Fe nanoparticles that are useful for catalytically activating hydrogen peroxide and decomposing contaminated soils can be synthesized from sorghum bran.

Magnetic resonance imaging, superparamagnetic relaxometry, sensors, and catalysis are among the fields that heavily rely on iron oxide nanoparticles. The nanoparticles need to be coated with materials such as alkyl-substituted amines for these applications. Compared to Fe nanoparticles made by chemical and physical means, those made utillizing a green chemistry approach have more bioactivity.

10. Cerium oxide nanoparticles:

With their antibacterial qualities, CeO_2 nanoparticles possess a broad assortment of applications in the biomedical industry. Gloriosa superba leaf extract and aloe barbadensis gel were utilized in its synthesis. Gas sensors, oxygen pumps, solar cells, diesel fuels, and solar cells all use CeO_2 as a combustion catalyst.

11. Cadmium sulfate nanoparticles:

Lactobacillus sp. and Saccharomyces cerevisiae was used to create these semiconductor-like nanoparticles. Enzymes such as Coriolus versicolor can help remove harmful metals from soils by converting toxic cadmium ions to non-hazardous cadmium ions.

12. Tin oxide nanoparticles:

These oxides are semiconductors that function as photocatalysts in the breakdown of specific organic substances. Their multifarious characteristics, including biocompatibility, antimicrobial, antibacterial, anticandidal, and cytotoxic effects, make them one of the most significant nanomaterials. The hydrothermal method, coprecipitation, sol-gel process, and other techniques can be used to create tin oxide nanoparticles. These nanoparticles are often employed in sensors and have applications in magnetic resonance imaging.

13. Indium oxide nanoparticles:

Indium (III) nitrate is a simple synthetic tool for creating indium oxide nanoparticles. Numerous studies have been conducted to produce different structured indium oxide materials for different applications, including nanotubes and nanowires. X-ray diffraction, Fourier transform infrared spectroscopy, and transmission electron microscopy are readily applicable methods for characterizing these nanoparticles. These nanoparticles are necessary for organic light-emitting diodes, solar cells, and photocatalysts. [32]

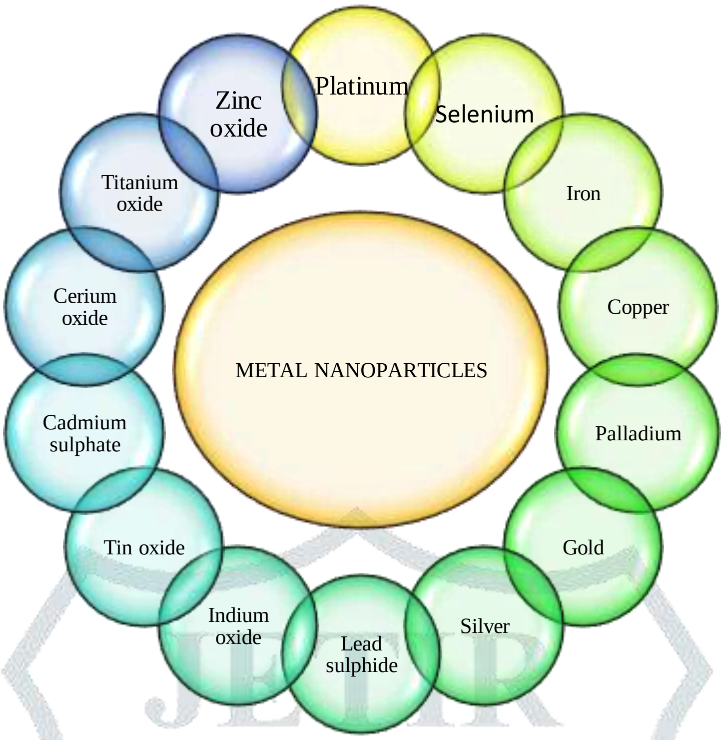

Fig. 4 Types of metal nanoparticles. [36]

Affectors on the various metallic nanoparticles' synthesis:

1. The impact of pH:

The pH value of the chemical reaction medium has a big impact on how nanoparticles develop. According to studies, adjusting the pH level of reaction media usually causes the produced nanoparticles to vary in size and shape. More specifically, bigger particles are usually generated at lower acidic pH levels than at higher pH values. For example, utilizing biomass from Avena sativa, or oats, rod-shaped Au nanoparticles produced at pH 2 were larger, ranging from 25 to 85 nm, and significantly smaller at pH 3 and 4, the particles are smaller (5-20 nm). The study discovered that between pH 3 and pH 4, the extract included more functional groups that were accessible and may be exploited for particle nucleation. On the other hand, the lack of accessible functional groups at pH 2 led to the particles aggregating and forming larger Au nanoparticles.

2. Reactant concentration effect:

The creation of metal nanoparticles can be significantly influenced by the quantity of biomolecules found in plant extracts. Huang et al. discovered that changing the amount of sun-dried camphor extract from leaves in the reaction fluid might have a significant affect on the morphology of the nanoparticles of gold and silver that were created. For example, when increasing amounts of extract were added to the precursor chloroauric acid, the resulting nanoparticles' form changed from triangular to spherical.

3. Reaction time's effect:

Reaction time is essential for the synthesis of nanoparticles, claims Ahmad (2012). Within two minutes of using Anana scomosus (Pineapple) extract for AgNP synthesis, there was a noticeable color shift and a quick reduction in the aqueous solution, which led to the formation of nanoparticles in the same amount of time. There was only a slight color shift following the reaction, which lasted up to five minutes. The resulting nanoparticles were round in form and had an average size of 12 nm. Ag as well as Au nanoparticles were made biogenically with leaf extract from Chenopodium album. The 2-hour reaction created the nanoparticles within 15 minutes of initiating the reaction, but very few larger-sized nanoparticles were synthesized during that time. [37]

4. Influence of reaction temperature:

Research has demonstrated that temperature also significantly influences the yield, size, and form of nanoparticles produced using plant extracts, despite the fact that reaction ambient temperature is widely recognized as a critical component of all synthesizers. For example, when Ag nanoparticles were created using sweet orange peels extracted at a reaction temperature, of 25 >C, particles with a typical size of about 35 nm were formed. However, when the reaction temperature was increased to 60 <C, the mean particle size decreased to 10 nm. Similarly, Song et al. used Diospyros kak (persimmon) leaf extract and a reaction temperature range of 25 to 95 ″C to create stable Ag nanoparticles. The average particle size drops, and the reaction and particle production rates seem to quicken as the reaction temperature rises, while the particle conversion rate increases continuously.[38]

APPLICATIONS AND TOXICITIES OF METALLIC NANOPARTICLES:

a) Metallic nanoparticle applications created using green technology:

Nanoparticles are often utilized in physicochemical and biomedical fields. In biomedical research, they can be applied to drug delivery, biosensing, bioimaging, and biomolecular recognition. Because of their anti-microbial qualities, these nanoparticles are included in many common products, such as deodorants, humidifiers, toothpaste, cosmetics, and water purification systems. They are essential to agricultural technology in areas like nutrient loss reduction to increase crop yields and plant disease detection and control.

1. Nanoparticles of silver and gold:

The variety of forms, sizes, and surface characteristics exhibited by Au nanoparticles offer notable benefits for their possible uses in biosensors, hyperthermia treatment, therapeutic drug delivery systems, genetic material delivery, and antibacterial medication delivery. By lowering aromatic nitrochemicals, rattlebush gold nanoparticles have shown catalytic action that can be useful in waste purification.

The potential of nanoparticles as novel medical instruments has been underscored by the emergence of antibiotic resistance in pathogenic bacteria. Since Ag has a well-established antimicrobial profile, it is frequently utilized in medical preparations to combat infections. AbNPs are frequently used in the food sector and healthcare. Because of their antimicrobial properties, they are suitable for a wide range of ecological purposes. It's important to keep in mind that not all of the evidence of silver toxicity has been extensively studied, even after decades of use. Both the medical field and alternative medicine have found uses for them. In addition to having silver integrated into their washing machines, some companies also use creams containing silver sulfadiazine to prevent burn site infections. Silver appears to be present in a lot of consumer goods these days, including computer keyboards, acne treatments, and clothes (like sportswear and socks) that stop their wearer from smelling like they do after using deodorizing sprays.

2. Copper and copper oxide nanoparticles:

CuO nanoparticles have shown great application potential by displaying antibacterial and antioxidant activity against typical pathogenic organisms, such as Staphylococcus aureus and E. coli. Their useful disinfecting abilities against a range of pathogenic pathogens enable them to function as bactericidal materials. Human lung cancer cells were found to be toxic to Cu nanoparticles made from Euphorbia nivulia stem latex (A549), suggesting a potential application in the therapy of cancer.

Additionally, palladium and platinum nanoparticles were investigated. A limited number of Pt nanoparticle-based catalysts demonstrate enhanced activity when applied to the electro-oxidation of formic acid in a clean environment.

3. Zinc oxide and titanium dioxide nanoparticles:

Adulticidal and larvicidal effects of TiO_2 suspensions against Bovicolaovis (sheep louse) and Hippobosca maculate (hematophagous fly) have been successfully investigated. Strongly antioxidant-behaving pathogens such as Aeromonas hydrophilic, E. coli, P. aeruginosa, and were confirmed to be effectively inhibited by TiO_2 nanoparticles derived from Psidium guajava extract. TiO_2 oxide nanoparticles have demonstrated potential uses in wastewater disinfection, the biomedical industry, and cosmetic products. A small number of catalysts based on Pt nanoparticles exhibit increased activity when used to electro-oxidize formic acid, which is used in clean environments.

Additionally, ZnO nanoparticles have antibacterial properties that have been applied to food packaging and wastewater treatment. Doxorubicin can be administered via biocompatible ZnO nanoparticles. Magnetite nanoparticles were employed in biomedical applications like position sensing, oscillation damping, and magnetic resonance imaging. In addition, the previously listed NPs possess an extensive array of non-medical uses, such as magnetic recording devices. [37]

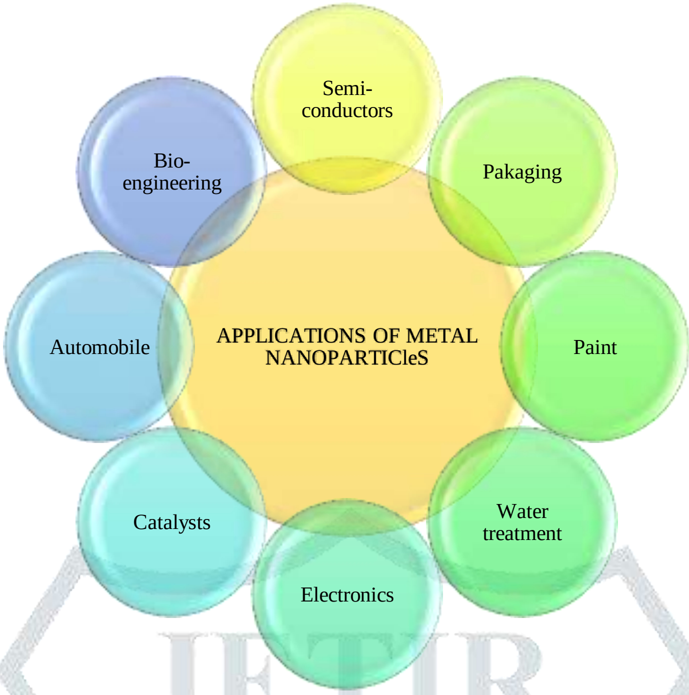

Fig. 5 Metal nanoparticle applications.[39]

b) Aspects of metallic nanoparticle toxicity:

Metal nanoparticle toxicity is linked to the activation of pro-inflammatory mediators, intracellular generation of reactive oxygen species (ROS), and oxidative stress reactions. This means that in addition to damage to DNA and proteins, lysosomal hydrolases, mitochondrial malfunction, apoptosis, damage to cell membranes, cytoplasmic disorder, , cell dysfunction can also be included. However, According to the dimension, kind, and personal, and combinations of particles, the harmful effects can change. Mechanisms of metal nanoparticle applications in biomedicine and the environment.[34]

Nanoparticles (NPs) are commonly uses in multiple industries, such as Electronic goods, farming, chemical compounds, medications, and foods, owing to their exceptional chemical and physical features. NPs have a wide range of uses in several industries, including electronics, agriculture, chemicals, medicines, food, and more, due to their unique physicochemical features. Nanoparticles of metal oxide, such as oxides of silicon ($SiO2$), dioxide of titanium ($TiO2$), oxide of zinc (ZnO), hydroxide of aluminum [$Al(OH)3$], oxide of cerium (CeO), oxide of copper (CuO), silver (Ag), nanoclays, nanotubes of carbon, and others, are among the most often employed NPs in many sectors. whereas the extensive release of Nanoparticles into the environment's air, water, as well as and land by many sectors is creating nanowaste, which is dangerous to life and disturbs the balance of ecosystems.

Nanoparticles are unhealthy for people as well as animals. Individuals who use NPs have an increased risk of developing bronchial asthma, diabetes, cancer, allergies, inflammation, and other illnesses. There have also been demonstrations of animal reproductive systems. to be affected by various NPs' toxicity, such as $TiO2$, Au, and others. Nanoparticles penetrate the internal organs of animals by ingestion and inhalation. They are subsequently picked up by cellular structures through the processes of endocytosis and phagocytosis, which result in the generation of reactive oxygen species (ROS) and ultimately damage to the mitochondria and lipid peroxidation, among other consequences. Furthermore, the overabundance of NPs is having an effect on the food chain within the ecosystem. The cytotoxic effect of NPs on plants, animals, and microbes is depicted in Figure 6. [40]

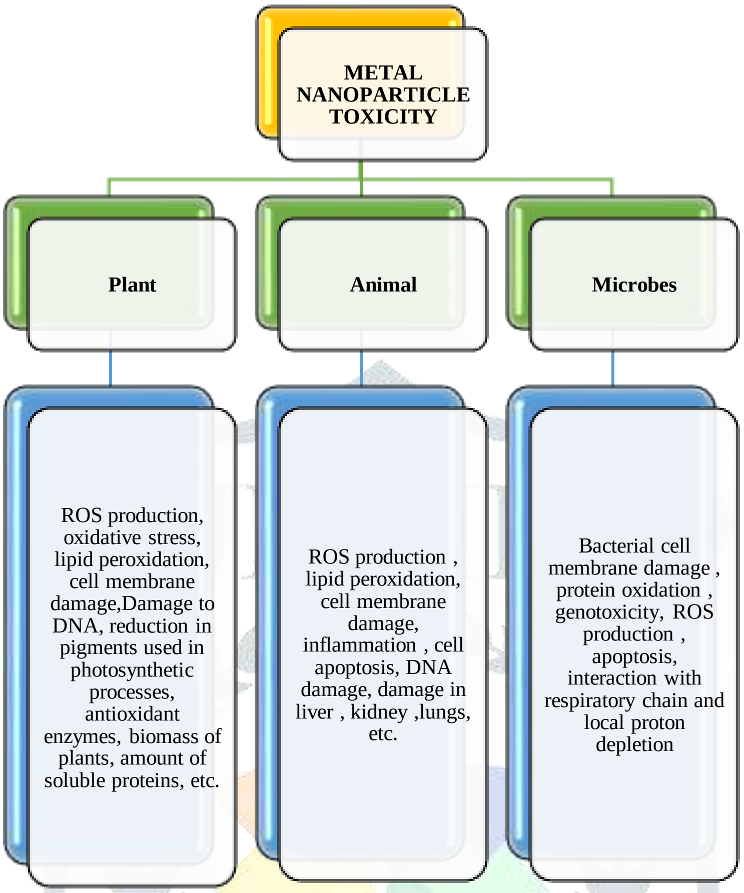

Fig. 6 Metal nanoparticle's toxic effects on plants, animals, and microbes. [40]

RECOVERABILITY AND REUSABILITY OF METAL NANOPARTICLES:

While it is crucial to stabilize and functionalize metal nanoparticles for a variety of applications, the scientific community is currently paying more attention to the simple and reasonably priced recoverability and, consequently, reusability of nanoparticles. Delivery, enzyme immobilization, protein, and cell separation have all benefited from magnetic separation for several years because it has particular advantages over other nanoparticle forms in terms of high efficiency, affordability, and speed. These days, magnetic nanoparticles (also known as magnetic nano-cores) are constantly showing up as heterogeneous supports in a variety of catalytic transformations, offering the added advantage of simple recoverability with a simple magnet, removing the need for catalyst filtration following the reaction or solvent swelling before it.[35]

SUMMARY ON SYNTHESIS OF METAL NANOPARTICLES BY VARIOUS PLANT SPECIES:

Plants Used	Nanopartical	Parts of Plant	Sizes	Plant Metabolites Involved in Bioreduction	Pharmacological Application
Acalypha indica	Ag, Au	Leaves	20-30	Quercetin, Plant pigment	antibacterial
Aloe vera	In_2o_3	Leaf	5-50	Biomolecules	Optical properties
Andrographis paniculata	Ag	Leaves	67-88	Alkaloids, flavonoids	Hepatocurati Activity
Alternanthera sessilis	Ag	Whole	40	Amine, carboxyl group	Antioxiant
A. Mexicana	Ag	Leaves	20-50	Protien	Antimicrobial
Caria papaya	Ag	Fruit	15	Hydroxyl flavones ,catechinins	antimicrobial
Boswellia serrate	Ag	Gum	7-10	Protien, enzyme	Antibacterial
Citrullus colocynthis	Ag	Calli	5-70	Polyphenols	Antioxidant, anticancer
Glesemium sempervirens	Ag	Whole	112	Protein, amide, amine group	Cytotoxicity
Lippia citriodora	Ag	Leaves	15-30	Isoverbascside compound	Antibacterial
Mentha piperita	Ag, Au	Leaves	90-150	Menthol	antibacterial
Mirabilis jalapa	Au	Flower	15-30	Polysaccharides	Antimicrobial
H. Canadensis	Ag	Whole	113	Phenolic, protein	Cytotoxicity

Iresine herbstii	Ag	Leaves	44-64	Biomolecules phenolic compound	Biological activity
Melia azedarach	Ag	Leaves	78	Tannic acid, polyphenols	Cytotoxicity
Tinospora cordifolia	Ag	Leaves	34	Phenolic compund	Antilarvicidal
Euphorbia prostrate	Ag	Leaves	52	Protein ,polyphenols	Antiplasmdial

Table 1. An overview of the different plant species production of metal nanoparticles [22]

MARKETED PREPARATIONS:

Product Name	Company	Drug	Nanopartical Manufacture Method	Final Dosage
Avinza®	King Pharma	Morphinesulfate	Wet media milling	Capsule
Azopat®	Alcon	Brinzolmid	Wet media milling	Suspension
Emend®	Merk	Aprepitant	Wet media milling	Capsule
FocalinXR®	Novartis	Dexmethylphenidate HCL	Wet media milling	Capsule
Invega Sustenna®	Johnson and Johnson	Paliperidone palmitate	Wet media milling	Suspension
Rapamune®	Wyeth	Siroliumus	Wet media milling	Suspension, Tablet
Triglide®	SkyePharma	Fenofibrate	High-pressure homogenization	Tablet

Table 2. Lists FDA-approved drug nanoparticle-based marketed products.[40]

MAJOR DIFFICULTIES AND FUTURE PERSPECTIVE:

In the most recent year, the study of nanoparticles and their potential uses has evolved quickly. Numerous studies have documented the greenly production of metal nanoparticles from a range of living resources, including microbes, mold, and yeasts. However, a number of problems still stand in the way of its widespread manufacture and subsequent applications. A list of some of the primary problems that arose throughout the synthesis is provided below:

• Every metabolite of plants extract and every component of microorganisms' cells should be thoroughly analyzed to find out what part they play in the synthesis of NPs.

• It is essential to give top priority to increasing the production of NP for commercial usage using green synthesis methods.

It is necessary to optimize different reaction parameters to improve the yield and stability of nanoparticles while reducing reaction time. Green synthesis methods for producing NPs on a large scale could become just as costly as traditional methods if these problems are fixed. The extraction and purifying of Nanoparticles through a mixture of reactions is an additional important problem that requires more investigation. It will take extensive toxicity studies on both plants and animals before NPs are employed in more fields. Apart from strains of the wild type, genetically modified microbes possessing enhanced abilities to synthesize enzymes, proteins, and biological molecules may also enhance nanoparticle manufacturing and stability. Furthermore, the enhanced ability of genetically engineered microbes to accumulate and tolerate metals may present a promising avenue for the green synthesis approach to creating and utilizing metal nanoparticles (NPs). [40]

CONCLUSION:

This review's main focus is on methods for green synthesis for metal nanoparticle preparation, including the uses of these methods and their clean, safe, and ecological alternatives to physiochemical methods for making metal nanoparticles. A variety of plant materials, including fruit extracts, seeds, bark, and leaves, as well as microorganisms, including bacteria, fungi, and actinomycetes, have shown the ability to synthesize various metals, including aluminum, silver, platinum, lead, nickel, selenium, copper, copper oxide, and titanium dioxide. Nanoparticle dimension, shape, as well as reaction rate are highly dependent on a variety of experimental factors, such as temperature, pH, reactant concentration, and reaction duration. To determine the morphology, dimension, as well as form of the biologically produced nanoparticles. Characterization methods such as AFM, X-ray diffraction, FTIR, scanning electron microscopy, transmission electron microscopy, EDX, and UV-VIS spectroscopy were employed. Because of this, the environment's buildup of these NPs and biological systems' absorption of them might have fatal consequences. Even though numerous studies have confirmed the green synthesis of metallic nanoparticles, further research is desperately needed to guarantee their successful commercialization and broaden their applications.

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